The amendment to Claim 24 removes prophylaxis from the claimed methods of treatment. The amendment responds to one of the grounds of rejection of the treatment method claims which the Examiner discussed at the interview. The matter will be further discussed below.

The amendment to Claim 48 inserts the concept of an effective amount of the active compound into the pharmaceutical composition claims. Since the compositions are described in the first line of that claim as "antiestrogenic or antiandrogenic", it is believed to be clear that the amount referred to is that which is effective to provide antiestrogenic or antiandrogenic activity. The amendment is in response to the rejection of Claims 48-62 under 35 U.S.C. 112 for failing to include an amount of drug, and is believed to avoid that rejection.

All of the amendments to the claims find good basis in the specification and are believed to raise no possible issue of new matter.

RESPONSE TO OFFICE ACTION

The Action which was mailed December 22, 1982 rejected Claims 1-62, all the claims in the case, under 35 U.S.C. 101, 103 and 112 on various grounds. Some of the grounds for rejection have been avoided by the amendments presented above. Reconsideration of all of the grounds for rejection is requested, in view of the amendments above and the remarks below, as well as the literature citations accompanying this Response, and withdrawal of the rejections is believed to be proper.

Applicant appreciates the courtesy of the interview which the Examiner granted to his representative on February 17, 1983. No agreements were reached at the interview, but the various grounds of rejection were discussed, and Applicant's representative gained a better understanding of the Examiner's position. The discussion below is directed to the points raised by the Examiner at the interview, as well as to those in the Action of December 22, 1982.

Claims 1-8, 11-12, 14 and 17-62 were rejected under 35 U.S.C. 103 as obvious over the Jones patent in the record. The Examiner stated that the prior art utility must be included in a showing, that only the Clemens Declaration deals with a utility taught by the Jones patent, and that the Clemens Declaration is defective in failing to state the number of animals in the treatment groups.

The enclosed Supplementary Declaration of Dr. Clemens supplies the missing information about the size of the treatment groups. Accordingly, Applicant submits that the proof of unexpected superiority of the present invention over the closest art is complete, and it is appropriate for the rejection under Section 103 to be withdrawn.

Applicant suggests, further, that the Examiner's statement, that the prior art utility must be included in a showing, is overly broad. It is believed that an applicant's burden is to show that the invention is unobvious, and that any and all appropriate evidence may be used. Applicant points, for example, to Ex parte Moiso, 212 U.S.P.Q. 294 (P.T.O. Bd. App. 1980), where the unexpected superiority of the invention in a number of different test systems was shown. The point of law is not vital to the present issue, however, since the Clemens Declaration does report a comparison of the invention with the art in a treatment method taught by the Jones patent, and clearly shows the superiority of the present invention in that use.

Method Claims 24-47 were rejected under 35 U.S.C. 101 because the claimed invention was said to lack patentable utility. The Examiner said that claims to methods of curing cancer must be based on more substantial data; he said that the claims are based on beliefs and expectations arising from the test data, and stated that prostatic cancer and breast cancer lack significance because different forms of cancer may affect those organs.

Applicant submits that the evidence and teaching in the specification, combined with the common knowledge of pharmaceutical chemists, show that the claimed method has utility in the meaning of patent law. The claimed treatment method will be discussed in some detail before the legal issues are addressed.

Claim 24 (from which all of the other method claims depend) describes a method of alleviating a pathological condition of an endocrine target organ, which condition is dependent or partially dependent on an estrogen or on an androgen. It is emphasized that the claimed treatment methods are thus limited to conditions which are at least partially estrogen-dependent or androgen-dependent. The limitation necessarily follows from the fact that the compounds of the present invention are antiestrogens and antiandrogens. Accordingly, the treatment of prostatic cancer and breast cancer are not claimed broadly, but only insofar as those forms of cancer are, respectively, at least partially androgen-dependent or estrogen-dependent. Other forms of cancer are specifically excluded.

The narrower method claims describe the treatment of two estrogen-dependent conditions of the breast, mammary cancer and fibrocystic disease, and two androgen-dependent conditions of the prostate, prostatic cancer and benign prostatic hypertrophy.

A generation ago, the treatment of cancer was classed as an incredible utility, along with growing hair on bald men and perpetual motion machines, and claims to it were not allowed without the most rigorous proof. As our understanding of the various types of cancer has grown, and more and more effective treatment methods have been discovered, cancer treatments have joined the mainstream of pharmacetical chemistry and claims are allowed on a showing of evidence of utility satisfactory to convince one of ordinary skill in the art. For example, see In re Jolles, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980) where compound and cancer

treatment method claims were allowed based on evidence from testing in laboratories animals in a test system recognized to be predictive. Cancer treatment claims are not believed to require "more substantial data" than other claims; they require data sufficient to satisfy those skilled in the relevant art, like all classes of utilities.

Applicant will explain the data which have been presented to support the method claims, and will present articles from standard journals which illustrate that one of ordinary skill in pharmaceutical chemistry would recognize that the data prove the utility of the claimed treatment methods.

The antiestrogenic aspect of the utility will be discussed first.

The various tests reported by Mr. Black in his Declaration show with extreme clarity that the invention has antiestrogenic activity of a high order. Further, the tests reported by Dr. Clemens show that a typical compound of the invention has excellent ability to reduce mammary tumors induced by treatment of the test animals with DMBA. Applicant submits that one of skill in the relevant art would observe the showings of antiestrogenic activity and DMBA tumor reduction, and would recognize from his knowledge of the art that activity against mammary cancer and fibrocystic disease follow from the exemplified activity. The following scientific articles prove the point. Copies are enclosed.

Jordan and Koerner, J. Endocr. 68, 305-11 (1976) states on its first page that the DMBA-induced tumor model is ideal for the evaluation of antiestrogenic drugs for the treatment of mammary cancer. That article, as well as Ward, Brit. Med. J. 1, 13-14 (1973) indicates the efficacy of tamoxifen, a well known prior art antiestrogen, in the treatment of mammary cancer. The articles show that treatment of mammary cancer with antiestrogens is known in the art, and that the DMBA-induced tumor is a predictive model for its evaluation. A third article which illustrates

the acceptance by the art of the DMBA model for the prediction of activity of antiestrogens against mammary cancer is Nicholson and Golder, Europ. J. Cancer II, 571-79 (1975).

The relationship between antiestrogen therapy and fibrocystic disease is taught by Ricciardi and Ianniruberto, Ob. & Gyn. 54, 80-84 (1979), which discusses the successful treatment of benign breast lesions with tamoxifen. Further, Jacquemier et al., Cancer 49, 2534-36 (1982) illustrates the relationship between estrogen receptor tissue, which is present in the breast, of course, and fibrocystic disease. Finally, the importance of fibrocystic disease is shown by Coombs and Lilienfeld, Preven. Med. 8, 40-52 (1979), which reports a large statistical study of many women with diagnosed benign breast diseases, of which the largest category was fibrocystic disease. The study showed that women with such benign breast lesions had a higher probability of developing mammary cancer than the general population.

The relationship between antiandrogenic activity and pathological conditions of the prostate is similar to the relationship between antiestrogenic activity and pathological conditions of the breast. The antiandrogenic property of the invention is reported in tests beginning at page 82 of the specification, as well as in Mr. Hanlin's Declaration, and it is believed to be clear that the tests show potent antiandrogenic activity. The enclosed articles by Stoliar and Albert, J. Urology 111, 803-07 (1974), and by Sogani and Whitmore, J. Urology 122, 640-43 (1979), report successful treatment of prostatic cancer with the antiandrogen flutamide (SCH-13521). These articles illustrate the belief of pharmaceutical chemists that antiandrogens are useful in treating prostatic cancer.

The activity of antiandrogens against benign prostatic hypertrophy is illustrated by the articles by Caine et al., J. Urology 114, 564-68 (1975), and by Geller et al., Geriatrics, 63-71 (1977). The Caine article

reports successful treatment of BPH with flutamide, and Geller used megestrol acetate, a progestational antiandrogen.

Thus, Applicant submits to the Examiner that the cited articles demonstrate that compounds with antiestrogenic and antiandrogenic properties are presently accepted as efficacious for the treatment of estrogen-dependent mammary cancer and fibrocystic disease, or for androgen-dependent prostatic cancer and benign prostatic hypertrophy, respectively. Thus, since the antiestrogenic and antiandrogenic properties of the present compounds have been proved, it appears that the claimed methods of treatment are in accordance with the present knowledge and theories of the relevant art, and therefore that the rejection under Section 101 is unnecessary and should be withdrawn.

At the interview, the Examiner expressed concern about the prophylactic aspect of the method claims. He expressed particular concern about the identification of the group at risk. Applicant has decided to cancel prophylactic treatment from his claims and the appropriate amendment is presented above, avoiding the ground of rejection.

SUMMARY

Applicant has submitted amendments, entry of which is requested, to Claims 8-16, 24 and 48. A Supplementary Declaration Under Rule 132 of Dr. Clemens is enclosed for the Examiner's consideration.

The Examiner is requested to reconsider and withdraw the rejection under Section 103 in view of the Supplementary Declaration, which completes the showing of activity against mammary tumors which was presented in Dr. Clemens' original Declaration.

The rejection under Section 101 has been thoroughly discussed, and articles illustrative of the present state of the art have been presented. The Examiner is requested to reconsider and withdraw that rejection, on the ground that the demonstrated activity of the compounds

is regarded in the relevant art as indicating that the claimed treatment methods would be useful.

The rejections under Section 112 have been met by appropriate amendments to Claim 48 and Claims 8-16. The Examiner is requested to reconsider and withdraw those rejections in view of the amendments.

Respectfully submitted,

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